REMARKS

The Invention

The present invention relates to a high-throughput method of distinguishing at least one molecule individually in a sample comprising multiple molecules. The one or more molecule(s) to be detected are not amplified prior to being subjected to electrophoresis. In keeping with the inventive method, the molecule to be detected is imaged and its electrophoretic mobility is determined.

The Pending Claims

Claims 1, 3-23, 57-65, and 67-91 are currently pending.

The Amendments to the Claims

Claims 21 and 83 have been amended to recite that the multiple molecules in the sample are not amplified prior to being introduced into the sample channel. These amendments are supported by, for example, originally filed claims 2 and 66, and by the specification at, for example, page 11, lines 9-12. Accordingly, no new matter has been added by way of these amendments.

The Office Action

The Office Action has made the following rejections:

(a) claims 1, 3-8, 10-13, 15-18, 65, 67-72, 74-76, and 78-80 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over U.S. Patent 6,485,625 ("the Simpson patent") in view of U.S. Patent 6,438,279 ("the Craighead patent"), and U.S. Patent 5,188,963 ("the Stapleton patent"),

(b) claims 9 and 73 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over the combined disclosures of the Simpson patent the Craighead patent, and the Stapleton patent in further view of U.S. Patents 6,221,592 ("the Schwartz patent") and 5,215,883 ("the Chu patent"),

(c) claims 14 and 77 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over the combined disclosures of the Simpson patent, the Craighead patent, and the Stapleton patent in further view of U.S. Patents 6,586,193 ("the Yguerabide patent") and 6,120,667 ("the Hayashizaki patent"),

(d) claims 19, 20, 81, and 82, are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over the Simpson patent in view of the Craighead patent and the Stapleton patent,

(e) claims 21, 22, 58, 60-62, 83, 84, 86, 88, and 89 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over the Simpson patent in view of the Craighead patent,

(f) claims 23, 57, and 85 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over the combined disclosures of the Simpson patent and the Craighead patent in further view of the Yguerabide patent and the Hayashizaki patent,

(g) claims 63, 64, 90, and 91 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over the Simpson patent in view of the Craighead patent,

(h) claims 59 and 87 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over the combined disclosures of the Simpson patent and the Craighead patent in further view of U.S. Patent 5,538,613 ("the Brumley patent").

Reconsideration of these rejections is hereby requested.

Discussion of Rejections Under 35 U.S.C. § 103(a)

Claims 1, 3-8, 10-13, 15-18, 65, 67-72, 74-76, and 78-80 are rejected under Section 103 as allegedly being obvious over the Simpson patent in view of the Craighead patent and the Stapleton patent. This rejection is traversed for the reasons set forth below.

The Simpson patent discloses a method for the detection of molecules in a sample, wherein the molecules to be detected are amplified via polymerase chain reaction (PCR) prior to electrophoresis and spectroscopic analysis (see the Simpson patent at, e.g., col. 6, lines 35-42, and col. 29, line 24, through col. 30, line 30). Thus, the Simpson patent describes the detection of many molecules of a single type. The Craighead patent discloses a method for detecting single fluorophore-labeled molecules (e.g., DNA) in a sample by electrophoresing the molecules in the sample through an integrated flow channel/optical waveguide device (see the Craighead patent at, e.g., col. 5, lines 48-57, and col. 7, lines 59-67). The Craighead patent further discloses measuring the velocity of each molecule moving through the flow channel one at a time (see the Craighead patent at, e.g., col. 7, lines 63-67, col. 17, lines 43-48, and claim 8). Neither the Simpson patent nor the Craighead patent discloses a method that can distinguish *at least one* molecule individually in a sample comprising multiple molecules, wherein the molecules are not amplified prior to being subjected to electrophoresis. The Stapleton patent is relied upon for its purported teaching of a method for analyzing nucleic acid samples that requires no amplification. In particular, the Office Action points to Figure 9 and col. 18, lines 19-25 as allegedly disclosing methods of analyzing nucleic acids without amplification.

All of the pending claims, as amended, relate to a method or a system which requires that the multiple molecules in the recited sample are not amplified prior to being introduced into a sample channel (e.g., an electrophoretic channel). Contrary to the assertion of the Office Action, the Stapleton patent does not cure the deficiencies of the combined disclosures of the Simpson and Craighead patents. In this respect, the Office Action has failed to analyze the Stapleton patent *as a whole*. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

As a whole, the Stapleton patent discloses a device for automated detection of nucleic acid sequences in biological samples. The biological samples are embedded in a matrix within the device, and the matrix is subjected to various analytical methods for nucleic acid detection, including *amplification*, electrophoresis, and probe hybridization (see, e.g., col. 3, lines 24-36). Indeed, the Stapleton patent states "[s]equence-specific nucleic acid identification depends upon one or more of the three fundamental methods: *amplification*, hybridization, and electrophoresis" (see col. 5, lines 58-62 (emphasis added)). The Office Action contends that Figure 9 of the Stapleton patent evidences nucleic acid sample preparation without amplification. Figure 9, however, is a diagram depicting the disclosed nucleic acid analytic method, and clearly state "amplification" as being part of that method. Moreover, the Examples of the Stapleton patent, with the exception of Examples 5 and 12, disclose methods which involve amplification of the nucleic acids within a sample. Examples 5 and 12 only prophetically disclose the *possibility* of DNA detection without amplification in instances where sufficient amounts of nucleic acid are present in the sample (see col. 16, lines 45-48, and col. 18, lines 19-21). Ultimately, then, Examples 5 and 12 suggest to one skilled in the art that the method disclosed therein is not capable of detecting at least one molecule in a sample without amplification.

A consideration of the cited references *as a whole* reveals that the presently claimed invention is unobvious over the combination of the cited references inasmuch as there is no teaching or reasonable suggestion in the cited references to combine their disclosures in the precise manner required to result in a method for the detection of at least one molecule individually in a sample comprising multiple molecules without amplification of the molecule to be detected.

Although the Office Action alleges that one of ordinary skill in the art would have been motivated to combine the teachings of the Simpson, Craighead, and Stapleton patents to use simpler samples that are not amplified prior to electrophoresis (see Office Action at page

3), neither the Simpson, Craighead, and Stapleton patents teaches the desirability of combining the teachings of the references, let alone in the precise manner necessary to provide the present invention. See *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990) "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." Absent the use of impermissible hindsight, one skilled in the art would not combine the diverse teachings of the cited references to arrive at the claimed invention. The Federal Circuit has held that combining prior art references without evidence of a suggestion, teaching, or motivation to combine the references, even where all elements of the claimed invention are taught in the prior art, "simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability –the essence of [impermissible] hindsight." *In re Dembiczak,* 175 F3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). The Federal Circuit emphasized that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing [i.e., actual evidence] of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2d at 1617. Moreover, the Federal Circuit held some time ago that "one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988). Accordingly, the invention defined by claims 1, 3-8, 10-13, 15-18, 65, 67-72, 74-76, and 78-80 is unobvious in view of the Simpson, Craighead, and Stapleton patents.

Claims 9 and 73 are rejected under Section 103 as allegedly being unpatentable over the combined disclosures of the Simpson, Craighead, and Stapleton patents in further view of the Schwartz patent and the Chu patent. The Schwartz patent and the Chu patent are relied upon solely for their purported teachings of photobleaching during nucleic acid sequencing and during electrophoresis, respectively. Neither the Schwartz patent nor the Chu patent satisfies the deficiencies of the other cited references as discussed above. Neither the Schwartz patent nor the Chu patent discloses a method for the detection of at least one molecule individually in a sample comprising multiple molecules without amplification of the molecule to be detected. Therefore, the combination of the Simpson, Craighead, and Stapleton patents in view of the Schwartz and Chu patents does not render obvious the invention defined by claims 9 and 73.

Claims 14 and 77 are rejected under Section 103 as allegedly being unpatentable over the combined disclosures of the Simpson, Craighead, and the Stapleton patents in further view of the Yguerabide patent and the Hayashizaki patent. The Yguerabide patent is relied

upon solely for its purported teaching of the use of equilateral prisms to enhance the signal to noise ratio in analyte assays, while the Hayashizaki patent is relied upon solely for its purported teaching of the use of a pinhole in an electrophoresis apparatus. Accordingly, neither the Yguerabide patent nor the Hayashizaki patent satisfies the deficiencies of the other cited references as discussed above. Neither the Yguerabide patent nor the Hayashizaki patent discloses a method for the detection of at least one molecule individually in a sample comprising multiple molecules without amplification of the molecule to be detected. Therefore, claims 14 and 77 are unobvious in view of the cited references.

Claims 19, 20, 81, and 82 have been rejected under Section 103 as allegedly being unpatentable over the Simpson patent in view of the Craighead patent and the Stapleton patent. Claims 19 and 20 depend upon claim 1, while claims 81 and 82 depend upon claim 65. Thus, claims 19, 20, 81, and 82 all relate to a method or a system which requires that multiple molecules in the sample are not amplified prior to being introduced into a sample channel. Therefore, for the reasons discussed above, the combination of the Simpson, Craighead, and Stapleton patents does not render obvious the invention defined by claims 19, 20, 81, and 82.

Claims 21, 22, 58, 60-62, 83, 84, 86, 88, and 89 have been rejected as allegedly being unpatentable over the Simpson patent in view of the Craighead patent. Claims 21, 22, 58, 60-62, 83, 84, 86, 88, and 89 depend from claim 1 or claim 65, either directly or indirectly. Thus, these claims all relate to a method or a system which requires that multiple molecules in the sample are not amplified prior to being introduced into a sample channel. Because the combination of the Simpson and Craighead patents does not disclose all the elements of claims 1 and 65, as discussed above, the invention defined by claims 21, 22, 58, 60-62, 83, 84, 86, 88, and 89 is unobvious over the Simpson and Craighead patents.

Claims 23, 57, and 85 have been rejected under Section 103 as allegedly being unpatentable over the Simpson and Craighead patents in further view of the Yguerabide patent and the Hayashizaki patent. The Yguerabide patent is relied upon solely for its purported teaching of the use of equilateral prisms to enhance the signal to noise ratio in analyte assays, while the Hayashizaki patent is relied upon solely for its purported teaching of the use of a pinhole in an electrophoresis apparatus. Neither the Yguerabide patent nor the Hayashizaki patent satisfies the deficiencies of the other cited references as discussed above. Therefore, claims 23, 57, and 85 are unobvious in view of the cited references.

Claims 63, 64, 90, and 91 have been rejected under Section 103 as allegedly being unpatentable over the disclosures of the Simpson and Craighead patents. Claims 63 and 64 depend upon claim 1, while claims 90 and 91 depend upon claim 65. Thus, claims 63, 64, 90,

and 91 all relate to a method or a system which requires that the multiple molecules in the sample are not amplified prior to being introduced into a sample channel (e.g., an electrophoretic channel). Therefore, because the combination of the Simpson and Craighead patents does not disclose all the elements of claims 1 and 65, the combination of the Simpson and Craighead patents does not render obvious the invention defined by claims 63, 64, 90, and 91.

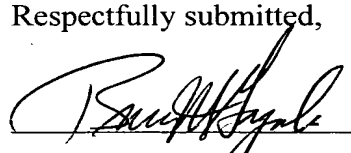
Claims 59 and 87 have been rejected under Section 103 as allegedly being unpatentable over the Simpson and Craighead patents in further view of the Brumley patent. The Brumley patent is relied upon in the Office Action solely for its purported teaching of the use of a microscopic objective lens in an electrophoresis analyzer. The Brumley patent, however, does not satisfy the deficiencies of Simpson and Craighead patents as discussed above. In this respect, the Brumley patent does not disclose a method for the detection of at least one molecule individually in a sample comprising multiple molecules without amplification of the molecule to be detected. Therefore, claims 59 and 87 are unobvious in view of the cited references.

In view of the foregoing, Applicants request that the rejections of the pending claims under Section 103 be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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